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Time to sputum culture conversion and determinants among MDR patients in Amhara Regional State Public Hospitals, September 2010 to December 2016: A multicenter retrospective follow up study

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June, 2017

Gondar, Ethiopia

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Abbreviation and acronyms

AFB	Acid Fast Bacilli
AIC	Akaike’ s Information Criteria
BIC	Bayesian Information Criteria
BMI	Body Mass Index
CHR	Crude Hazard Ratio
CS	Cyclo-Serine
CXR	Chest X-ray
DM	Diabetic Mellitus
DOTS	Direct Observed Therapy short coarse
ETHO	Ethionamid
HGB	Hemoglobin
HIV	Human Immune Deficiency Virus
HPF	High Power Field
HR	Hazard Ratio
Kg/m2	Kilogram Per Meter Square
KM	Kaplan Meier
LFX	Levofloxacin
LPA	Line Prove Assay
MDR	Multi Drug Resistant
PI	Principal Investigator
PAS	Paramino Salicylic Acid
PRO	Prothionamide
TB	Tuberculosis
TIC	Treatment Initiating Center
UOGRH	University of Gondar Referral Hospital
WHO	World Health Organization
XDR	Extensive Drug Resistant
Z	Pyrazinamide

Abstract

Introduction: In Ethiopia, MDR-TB is one of public health problems which need great emphasis. Time to sputum culture conversion is often used as an early predictive value for the final treatment outcome. Despite, guidelines for MDR prepared every time, medication providing freely and centers for MDR expanded, studies on time to culture conversion is very limited in Ethiopia. This study will give insights to policy makers, planners, clinicians and researchers.

Objective: The aim of this study was to determine time to sputum culture conversion and determinants among MDR TB patients in Amhara Regional State public Hospitals.

Methods: An institution based retrospective follow up study was conducted and 392 MDR TB patients were included in the study. Data were entered in to EPI info version 7.0 and transferred to Stata version 14 for further analysis. The proportional hazard assumption was checked. Parametric survival analysis, both univariate and shared frailty model were computed. Cox Snell residual was used for goodness of fit and AIC for model selection.

Result: A total of 340(86.7%) patients changed their initial sputum culture during the follow up period. The cumulative proportions of surviving on initial regimen were 89% at the end of one month, 56% at the end of two month, and 19% at the end of four month. Alcohol drinking (AHR=3.79, 95%CI=1.65-8.68), Sputum smear grading +2 (AHR=0.39, 95%CI 0.19-0.79), smear grading +3 (AHR=0.30, CI=0.14-064), cavitations (AHR=0.36, 95%CI=0.19-0.68), and consolidation (AHR=0.29, CI=0.13-0.69) were significant and independent predictors of time to sputum culture conversion.

Conclusion and recommendation: In this study time to sputum culture conversion was rapid. Alcohol drinking, sputum smear grading, cavitations and consolidation were found to be independent predictors of time to sputum culture conversion. Therefore, it is recommended to provide special attention to patients who had baseline radiological finding, high bacillary load and those who had history of alcohol intake at the baseline.

Key words: Time, MDR, culture conversion, Parametric, Survival analysis, Frailty model, Amhara Region, Ethiopia

1. Introduction

1.1 Statement of problem

Globally, tuberculosis (TB) is the second leading cause of morbidity next to human immune deficiency virus (HIV), and kills approximately 2 million people per year(1).

Multi drug resistance (MDR) TB is an increasing global problem (2).About480,000 new cases of MDR TB were estimated in 2014. Of this only 136,000 cases were officially diagnosed, 48% complete treatment, and 9% were develop extensively drug resistant (XDR) tuberculosis(3, 4). The impact of TB is worsen in Asia and Africa(5).About 88% of the anticipated MDR-TB cases found in Brazil, China, India, the Russian Federation and South Africa(4). According to 2014 global report 28% of MDR TB patients were found in the African Region (6), and Ethiopia ranked 15th among the 27 high MDR-TB burden countries; with more than 5000 estimated MDR-TB patients each year. The prevalence is 2.8% and 21% in newly diagnosed patients and in retreatment patients respectively (7). Since, the risk is high among previously treated patients, proper treatment and enhancing case detection is needed to ensure good success rate and halt the emergence of MDR/XDR TB (8).

Treatment of MDR TB takes 2 years (18-24 months) and monthly sputum culture is considered as a remarkable indicator of treatment effectiveness, especially during the intensive phase of treatment (9).Culture conversion on MDR TB patient is considered a reliable indicator of non-infectiousness and defined as two consecutive negative sputum cultures taken at least 30 days apart following an initial positive culture(10).

In a recent review including 22 studies, the proportion with culture conversion ranged from 52% to 95% (the majority were <80%), the median or mean time to culture conversion ranged from 35 days to 5 months, and the majority of patients' sputum cultures converted within 2 months (11). Knowing time to Sputum culture conversion is often used as an early predictive value for the final treatment outcome, especially in MDR TB patients (12).

The most common Factors that affect time to sputum culture conversion are: MDR category, HIV co-infection, presence of radiological finding, presence of chronic

disease, number of resistant drugs at the initiation, number of active drugs taken, and therapy delay greater than one month(13-16).

Delaying sputum culture conversion is resulted in economic wastage by prolonging the duration of treatment, poor treatment adherence and consequently treatment failure. It is also associated with higher case fatality rates (50 - 80%) as a result of drug toxicity leading to the emergence of XDR-TB(16).

The Ethiopian government applied Administrative, environmental, personal respiratory protection measures (N95 especially in all MDR centers for patients and health professionals), expansion of MDR centers and DOTs strategy to minimize the high burden of MDR tuberculosis. However, the prevalence of MDR-TB in Ethiopia is not decreasing as expected (7).

Despite, provision of free treatment, monthly culture monitoring, and expansion of services, studies on time to sputum culture conversion in our country including the study area is very limited. Therefore, this study aimed to determine time to sputum culture conversion and its predictors among MDR patients.

1.2. Literature review

1.2.1. Time to sputum culture conversation

Culture positive MDR patients once they initiated on Drug resistance TB treatment; there culture is expected to be negative at one point in time in order to have a good treatment outcome. Early conversion is a supreme important in the final treatment outcome and a patient may cure, treatment completed, die, lost to follow up(LTFU), develop treatment failure or he or she may transferred to another facility or they might alive in chronic complication.

Different studies assessed rate of culture conversion among MDR TB patient in different way with respect to Socio-demographic, behavioral and Clinical characteristics. A multi centered retrospective follow up study conducted in Russia, Peru, Latvia, Estonia, and Philippines showed that 85.4% of patients were converted their culture within two to five months. The median conversion time was 3.0 months (11). According to a study conducted in Latvia 77% of MDR Tb patients were culture negative at the end of 2 months. The median initial sputum culture conversion time was 83 days(17). One study conducted in Pakistan among MDR TB patients showed that the median culture conversion time was 196 days with cumulative probability of 6%,33%,47%,and 73% at 2,4,6, and 8 months respectively (18). A retrospective follow up study conducted in India revealed that 83%were become culture negative. The median time to initial sputum culture conversion was 91.3 days. Among these 57%, 73%, and 79% become culture negative at the 3, 4, and 6 month respectively (19).

A prospective study conducted in Georgia showed that 70.7% had culture conversion and the median conversion time was 68 days. According to a study conducted in Peru the overall culture conversion rate were 87.7% and the median initial culture conversion time was 59 days. Of these, 92.5% had culture conversion within 6 month (20).

According to World health organization 2014 report African Region accounts 28% of the world MDR burden and relatively it was the sever form. South Africa alone accounts 87% of MDR burden in the Africa region(21).

A study conducted in South Africa revealed that 88% of participants were converting their culture within the first six month. The overall median conversion time was 62 days (22).

Ethiopia is one of the high burden TB countries with expected incidence rate of 261/100,000, mortality rate of 35/100,000 and ranked 15 among 27 high burden MDR TB cases (23).However, there is no study done on time to sputum culture conversion and associated factors in Ethiopia.

1.2.2. Factors affecting sputum culture conversion time

Time to sputum culture conversion among MDR patients were vary within individuals. This variation mainly affected by the socio demographic, behavioral, and clinical factors.

Socio demographic factors

Sex of MDR TB patient is an important predictor for time to initial sputum culture conversion. In the study conducted in Indonesia revealed that being female was associated with longer duration of culture conversion time. However, a study done in Turkey among MDR TB patients revealed that being male has an effect in prolonging initial time of culture conversion (24).Age of the respondent had also an effect in MDR TB culture conversion time. According to this study old age had a significant effect in time to sputum culture conversion (24).

Behavioral factors

Behavioral factors like drinking alcohol, smoking and chat chewing are among the common behavioral factors affecting sputum culture conversion time. As studies showed that currently smoker MDR TB patients had better conversion time as compared with nonsmoker, but there is no difference in overall treatment impact (25). However, another study in Pakistan and Georgia indicated MDR TB patients who were smoker had longer time to sputum culture conversion as compared with nonsmokers (18, 26).

A multi-center study conducted in five world countries by communicable and diseases control (CDC), America showed that alcoholic MDR TB patients were significantly associated with less conversion rate (delayed conversion time) (11).

Clinical factors

Different studies revealed that severely underweight patients whose Body Mass Index (BMI)<16 kg/m(2) had longer initial conversion time as compared with MDR TB patients with normal BMI and the probability of conversion within 4 month is low (18, 19, 27). Similarly, MDR TB patients with BMI less than 18.5 kg/m(2) resulted in prolonging the 3 month sputum culture conversion as compared with patients with normal BMI(28). In MDR TB patient's variety of co morbid conditions like Diabetic Mellitus (DM), HIV, and anemia affect the conversion time and usually associated with prolonging of culture conversion time. Patients with HIV infection or DM had marginally better conversion rate than pulmonary tuberculosis patients without any co-morbidity (8).

Whereas, in a study conducted in Georgia MDR TB patients with DM had longer time for sputum culture conversion as compared with non-diabetic patients (26). However, another study in Georgia showed that the rate of culture conversion is similar among MDR TB patients with DM and without DM (25). A multi-center study conducted in five world countries by CDC America revealed that MDR TB patients having previous history of TB treatment were statically significant to time of culture conversion and resulted in prolonging conversion time (11).

Different studies revealed that base line radiological findings like consolidation, cavitations, infiltration, and pleural effusion had an effect on MDR TB treatment outcome and prolonging the time to sputum culture. A study done in South Africa showed that presence of lung cavitations or infiltration at baseline on chest X-ray had significant effect in prolonging sputum conversion time among MDR patients (29-31).

Another study conducted in republic of Korea revealed that having MDR and XDR was significantly associated with longer duration of culture conversion time as compared with drug susceptible patients and other drug resistant (not both Rifampin and Isoniazid). This means patients having large number of inactive drugs is significantly associated with prolonging the duration of culture conversion and negatively affect the treatment outcome. (32).

Baseline sputum smear grading is an important predictor to time to sputum culture conversion as study done in Indonesia showed. According to this study MDR TB

patients with high bacillary load (+2 or +3) were resulted in delayed sputum culture conversion (33), Latvia (17) and Korea (34).

Generally, initial times to culture conversion among MDR TB patients were vary from patient to patient. This variation was contributed by different socio demographic, behavioral, and clinical factors. Majority of the studies were done in Asia, Europe and America. In Africa (31)only few studies were done and many of these studies used simple binary end point to identify determinants of initial culture conversion time.

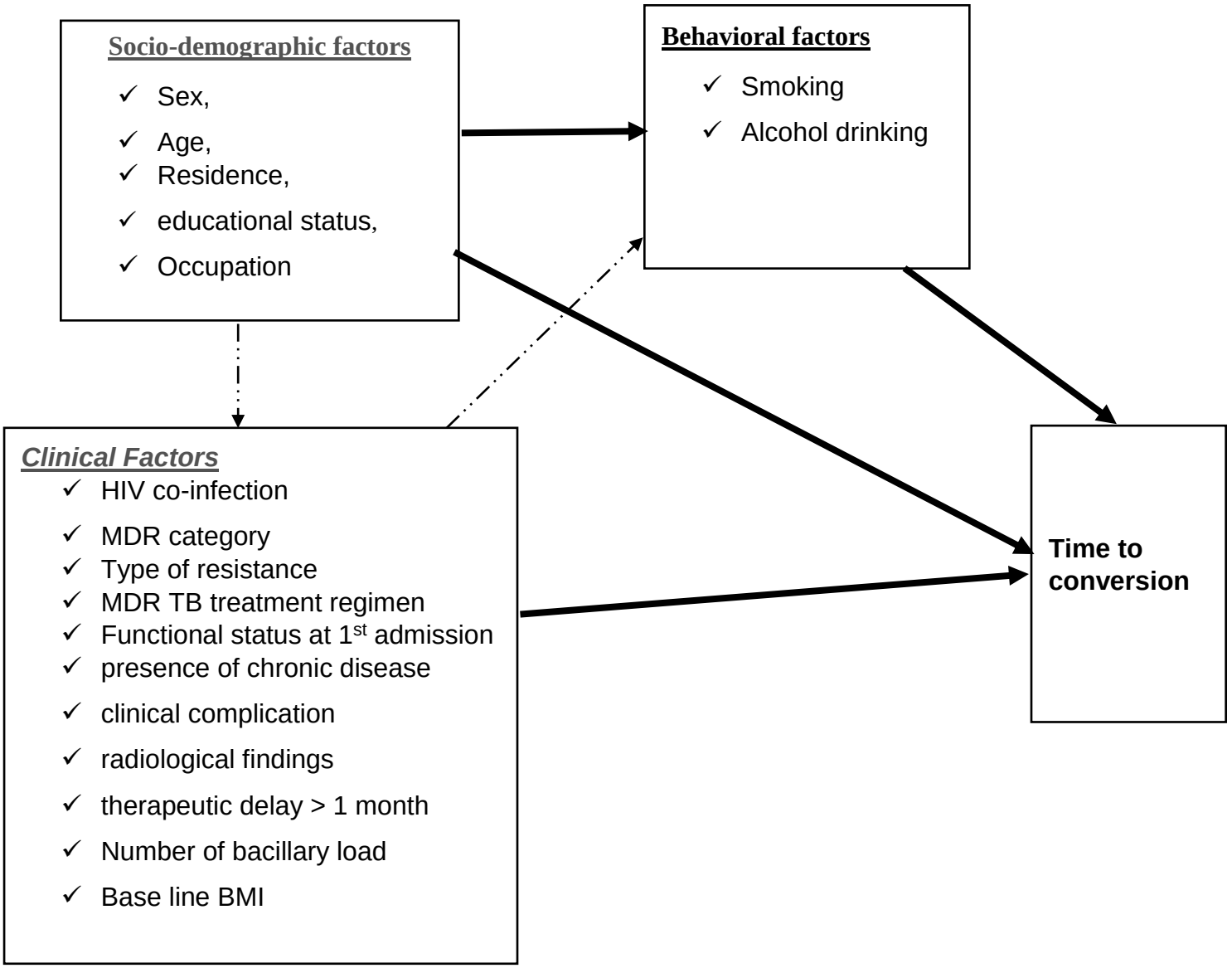

Figure 1 Conceptual framework of variables that have effect on time to sputum culture conversion (adopted from review of literatures) (9, 13, 26, 27, 30, and 33)

Justification of the study

The treatment of MDR-TB in Ethiopia started recently. Sputum culture conversion is a useful and appropriate interim indicator of treatment outcome in patients with multidrug-resistant TB. Multi drug resistantTB patients with rapid sputum culture conversion are a good indicator of good prognosis and minimize the communicability period. This further minimizes the overall burden of the disease. However, there is limited evidences on time to sputum culture conversion and associated factors in Ethiopia including the study area.

In this study, unobserved heterogeneity were considered for best estimation using frailty survival analysis. Studies on some important factors like educational status and residency were not addressed in the previous studies.

Similarly, this study will be crucial to policy makers, clinicians, and even for researchers as a base line. Hence, the objective of this study is to assess time to sputum culture conversion among a cohort of MDR-TB cases and to assess risk factors influencing their conversion time.

2. Objectives

2.1. General objective:

- To determine time to sputum culture conversion and determinants among MDR TB patients in Amhara Regional State Public Hospitals, Ethiopia.

2.2 Specific objectives

- To determine time to sputum culture conversion among MDR TB patients in Amhara National Regional State
- To identify determinants of sputum culture conversion among MDR TB patients

3. Methods

3.1. Study design and period

Institutional based retrospective follow up study was conducted from September 2010 to December 2016 among MDR TB patients in Amhara Regional State Public Hospitals.

3.2. Study setting

University of Gondar referral hospital, Borumeda hospital and Debre-Markos referral hospitals were selected among the nine hospitals in the region, which provide MDR treatment service, as about 70% of patients enrolled at treatment initiating centers (TIC).

University of Gondar referral hospital is the second hospital Next to St. Peter Hospital; which started MDR TB treatment in September 2010 as pilot program with Global Health Commute (GHC) approval to treat patients for the national response to the emerging threat of drug resistance TB.

University of Gondar referral hospital is located in North Gondar administrative zone, Amhara National Regional state, which is far from about 750 km Northwest of Addis Ababa (the capital city of Ethiopia). According to the 2015 population projection for major cities in Ethiopia, the total population size of Gondar town was estimated to be 323,900. Currently Gondar town has one Referral Hospital (UOGRH), eight Health Centers, and fourteen health posts which is government owned; there is also one general Hospital, thirteen specialty clinics, fifteen medium clinics, and ten primary clinics run by private sectors. University of Gondar hospital is a teaching Hospital which serves more than five million people of the North Gondar zone, peoples of the neighboring zones and some part of Tigray region. It gives service for 313 MDR patients starting with the inauguration.

The second setting is Debre-Markos Referral Hospital which is located in Debre Markos town (a capital of east gojjam). It is 297 km far from Addis Ababa and 264 km away from Bahirdar, which is the capital of the region. Besides to other services MDR center is established in the town recently and has given service for 50 MDR patients.

The third setting is Borumeda, which is located 10 km far from Dessie, which is the capital of south wello and 441 km far from Addis Ababa. Its center was established in 2013 and it has given service for 131 MDR patients.

3.3. Source and study population

All pulmonary MDR TB patients who were following their treatment in Amhara National Regional State hospitals were considered as a source population. Whereas, all pulmonary MDR TB patients who were culture positive at the initiation of treatment in the three selected hospitals were considered as a study population.

3.4. Inclusion and Exclusion criteria

Inclusion criteria: All Drug resistance TB patients who were culture positive at the start of treatment at least for two month and have follow up at UOGRH, Debre Markos, and Borumeda hospitals from 2010-2016 were included in the study.

Exclusion criteria: Patients who have incomplete data on the outcome variables were excluded. Culture positive MDR patients who were follow less than two months and MDR TB patients who were culture negative at the start of the study were also excluded in the study.

3.5. Sample size and sampling procedures

3.5.1. Sample size determination:

Initially, University of Gondar referral hospital, Debre Markos hospital, and Borumeda hospital were selected. Because these hospitals were the 1st in providing treatment and had the largest number of patients and assumed to be representative of the region. According to a retrospective follow up study conducted in Pakistan to assess time to sputum culture conversion and associated factors being female (CHR=1.93), current smokers (CHR=0.2),prior history of 2nd line drug use (CHR=0.39) and age> 40 years (0.48) were used to estimate the sample size (35).

Estimated sample sizes for two-sample comparison of survivor functions Log-rank test, Freedman method is used with the following considerations;

STATA version 14 is used for sample size determination.

Table 1: Sample size comparison using Log-rank test Freedman method

Outcome	Proportions	Withdrawal probability	Power	Final sample size
Time to conversion	0.73 at 8 months	5%	80%	358
Predictors	**Assumptions**	**Proportion**	**HR**	**Sample size**
Female sex	*Power=80%* *1:1(ratio), wdprob=5%*	0.73	1.93	228
Current smoker	*Power=80%* *0.077(ratio), wdprob=5%*	0.73	0.2	165
Age>40 years	*Power=80%* *1:4(ratio), wdprob=5%*	0.73	0.48	146
Prior 2nd line drug	*Power=80%* *1:5(ratio), wdprob=5%*	0.73	0.39	123

According to the sample size calculation, we used the largest of all which is 358. Therefore, the total number of sample in this study was 358. However, the total number of cases which fulfilled the inclusion criteria was 392.

3.6. Variables of the study

3.6.1. Dependent variable

- ✓ Time to sputum culture conversion

3.6.2. Independent variables

Time to sputum culture conversion is affected by different factors which include socio-demographic, behavioral and clinical factors which are listed below.

- ✓ **Socio-demographic characteristics**: Sex, age, residence, educational status, and marital status
- ✓ **Behavioral factors**: Smoking, alcohol drinking
- ✓ **Clinical characteristics:** HIV co-infection, MDR category, MDR treatment regimen, type of resistance, presence of chronic disease, clinical complication, radiological findings, therapeutic delay > 1 month, base line BMI, smear grading and functional status.

3.7. Operational Definition

Time to sputum culture conversion- is a time from the initiation of treatment of MDR TB to a patient had 2 negative consecutive cultures taken at least 30 days apart after initiation of treatment.

Censored- when the outcome of interest has not been observed for an individual this includes treatment stopped while culture is positive, died before conversion, transfer out before conversion and study time completion before culture conversion.

Cohort - Group of patients diagnosed and registered for MDR-TB treatment.

Therapeutic delay – A confirmed MDR-TB patient who starts treatment after one month of MDR TB diagnosis

Previously not treated for TB A patient who denies having had any prior anti-TB treatment or taking anti TB less than one month.

Previously treated case - A patient who were treated for TB for one month or more

BMI–Low BMI: A patient who had under <18.5 kg/m2 body mass index

Normal BMI: A patient who had ≥18.5kg/m2 body mass index:

Acid Fast Bacilli (AFB): Sputum smear microscopy was performed at baseline and on monthly follow-up using Ziehl- Nielsen staining. Results are reported based on the number of acid-fast bacilli (AFB): negative (no AFB/ 100 high-power fields [HPF]), scanty (1–9 AFB/100 HPF), 1+ (10–99 AFB/100 HPF), 2+ (1–9 AFB/HPF) and 3+ (.>9 AFB/HPF).

3.8. Data collection procedures and quality control

3.8.1. Data collection procedure

Prior to data collection, the records were reviewed (both baseline and follow up records) were identified by their medical registration/card number. Then data collectors were reviewed and extract data from patient charts and registries using a semi structured check list. Data extraction check list were prepared in English from patient's card.

3.8.2. Data collectors

Nine health care professionals (nurse and health officer) collected the data. Four data collectors in Gondar, three for Borumeda and two for Debre Markos were involved in data collection.

3.8.3. Data quality control

Training on the objective of the study and how to review the documents as per the data extraction format were given to data collectors. The PI supervised the overall process. The filled formats checked for completeness by the PI and three supervisors.

3.9. Data processing and Analysis

The data were entered in to EPI info version 7 and exported to Stata version 14 statistical software for further analysis. Baseline weight and height which was taken from the registration book were used to calculate BMI. Then BMI was computed by **weight/ (height)** ^{2}.

Descriptive summary statistics like median survival time, Kaplan Meier curve survival estimation and Log rank test were computed.

Proportional hazard assumption was checked both graphically and hypothesis test called Schoenfeld residual test which assessed the relationship between the scaled Schoenfeld residuals and time. Schoenfeld residuals test (global test) showed that PHA was satisfied. At the same time Schoenfeld residual test was done for all variables and all met the proportional hazard assumption.

After proportional hazard assumption checked; Cox regression model for bivariable and multi variable analysis were done. After fitting the Cox regression model AIC and BIC were estimated for model comparison. Then, parametric, and frailty models were done for time to sputum culture conversion to identify the potential determinants.

Hazard ratio is used as a measure of the probability of culture conversion, assuming that the Survival model is usually expressed in terms of hazard function.

Once Cox regression model fitted, parametric survival analysis model were fitted by considering the baseline hazard with different distribution assumption. Under the parametric approach, the baseline hazard is defined as a parametric function and the vector of its parameters are estimated together with the regression coefficients and the frailty parameter(s).

i). Baseline Exponential Distribution

The exponential distribution, with only one unknown parameter and it is the simplest of all life distribution models. In the exponential model, the conditional probability is constant over time. In other words, the main feature of exponential distribution is that the instantaneous hazard does not vary over time. The hazard function under this model is to assume that it is constant over time.

ii). Baseline Weibull Distribution

Weibull distribution is one of the parametric distributions which are used for the analysis of survival data. The Weibull distribution is more general and flexible than the exponential distribution and allows for hazard rates that are non-constant but monotonic.

Sometimes there may be heterogeneity, due to unobserved covariates added to the measurement error of observed covariates. Thus frailty model takes this into account to give a random effect model for time-to-event data, by adding a frailty term, Z. There are two types of frailty (Univariate and multivariate (shared frailty) model). Univariate frailty

assumes there is unknown covariates exist across an individual level and shared frailty model considers individuals in the same cluster have the same frailty and differ across the groups.

Then both univariate and shared frailty model were tested by considering different parametric distribution and frailty distribution (gamma and inverse Gaussian). A more parsimonious hazard model was chosen by means of the log likelihood ratio (LR) test and Akaike Information Criterion (AIC). Thus in the case of a comparison between models, we compared using both log likelihood ratio test and AIC value. The best fitted model was chosen using AIC and those having the smallest AIC were considered as a best fitted model. Similarly, goodness of model fitness also checked using Cox Snell residual test.

3.10. Ethical considerations

Ethical clearance was obtained from Institutional Review Board of University of Gondar. Supportive letter was received from Amhara Regional Health Bureau then permission letter was obtained from the hospitals administration and the MDRTB focal persons in UOGRH, Debre Markos and Borumeda hospital. Name of patients were not included during data collection. Questionnaires kept securely in locked cabinets and the data base entered into soft-wares was password protected.

4. Result

4.1. Baseline socio demographic characteristics of patients on MDR TB treatment

About 428 pulmonary MDR patients were reviewed. Among this 36 (8.4%) were excluded from the study because of baseline negative culture and contaminated result. Thus a total of 392 (91.6%) study units were included in the analysis. The majority of patients were attended at University of Gondar referral hospital 242(61.7%) followed by Borumeda hospital 113(28.8%), and the remaining were from Debre Markos hospital **(Figure 2).**

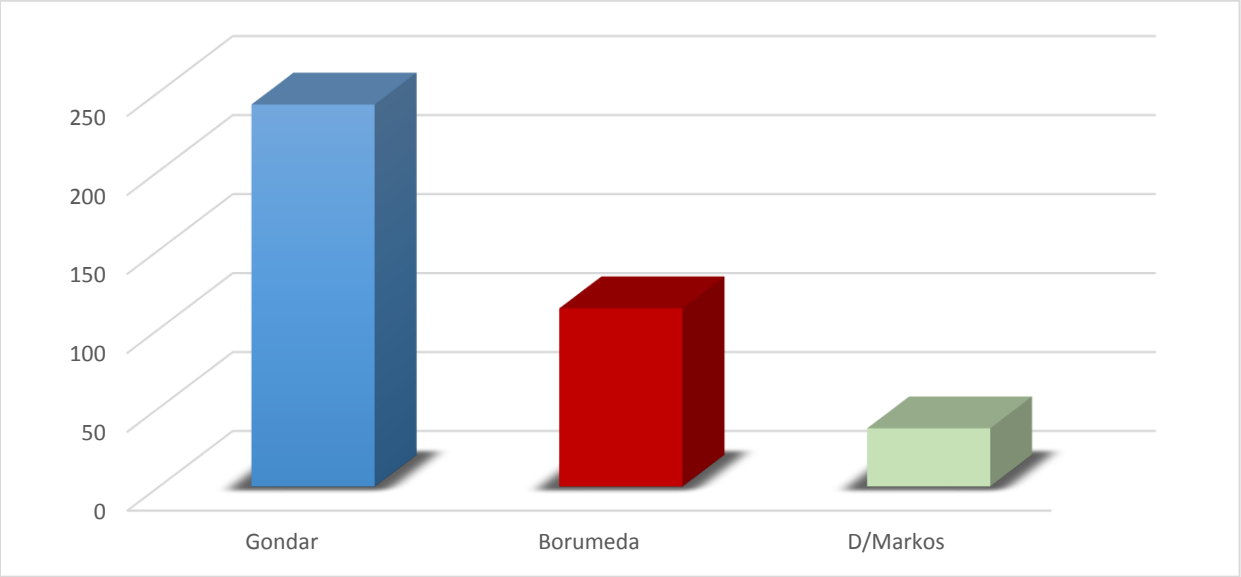

Figure 2 The Frequency distribution of number of MDR TB patients in Amhara Regional State Public Hospitals, September 2010 to December 2016.

Out of 392 participants, the median age of MDR TB patients at the initiation of MDR TB treatment was 29.5 years IQR (20-40 years). One-third of the participants 127 (32.4%) were under 25years. More than half of the respondents 228(58.2%) were males and about half of the respondents 200(51%) were urban dwellers. About 168(42.9%) were private workers and 314 (80.1%) were orthodox Christian's. Around 40% of MDR TB patients were not formally educated and 164 (41.8%) of respondents were married **(Table 2).**

Table 2: Baseline socio demographic and behavioural characteristics of MDR TB patients at initiation of MDR treatment in Amhara regional State Public Hospitals, Sep 2010 to December 2016 (n=392).

Variables	Frequency	Percentage
Age		
<=24	127	32.4
25-34	126	32.2
35-44	73	18.6
>45	66	16.8
Sex		
Male	228	58.2
Female	164	41.8
Place of residence		
Urban	200	51.0
Rural	192	49.0
Occupational status		
Unemployment	89	22.7
Governmental	36	9.2
Private	168	42.9
Daily laborer	37	9.4
Student	40	10.2
House wife	22	5.6
Religion		
Orthodox	314	80.1
Muslim	72	18.4
Other	6	1.5
Educational status		
No formally educated	156	39.8
Grade 1-8	12	31.6
Grade 9-12	74	18.9

Variables	Frequency	Percentage
Tertiary and above	38	9.7
Marital Status		
Married	164	41.8
Never married	135	34.4
Divorced	50	12.8
Widowed	8	2.1
Separated	35	8.9
Baseline Smoking		
Yes	56	14.3
No	326	85.7
Baseline Alcohol drinking history		
Yes	77	19.6
No	312	80.4

4.2. Baseline clinical status of the study participants

Among 392 MDR TB patients,9.9% had chronic disease. Of these 12 (3.1%) had DM and 4 (1%) had HTN. About one fourth (25.8%) of MDR TB patients had HIV co-infection .Among HIV positive patients, 95(94.1%) were on ART. Of these, 64.7% MDR TB patients were stage III and 33.3% were stage IV at the start of MDR treatment. Whereas, no patient were at stage one at the beginning of MDR TB treatment and the remaining 2 (2.0%) were start at stage II.

Majority of MDR TB 272(69.4%) were ambulatory and 376 (95.9%) hospitalized at the initiation of treatment. About 11 (2.8 %) of participants had previous MDR TB treatment and nearly half 50.8% of participants were mono resistance (Rifampin resistance). Regarding on x-ray finding, 107 (27.3%) of MDR TB patients and 160(40.82%) of participants had infiltration and cavitations respectively.

About 286 (73.0%) of participants had low BMI (<18.5kg/m2) and 7 (1.8%) of MDR TB patients had treatment modification. Among the 7 MDR TB patients 5 were due to MDR TB treatment failure suspect, one patient due to XDR TB confirmed and one due to life threatening drug side effect. Regarding with history of previous TB treatment,350 (89.3%) were previously treated for TB**(Table 3).**

Table 3 Baseline clinical status of MDR TB patients at the initiation of treatment, in Amhara Regional State Public Hospitals, September 2010 to December 2016.

Clinical factors	Frequency	Percentage
HIV co-infection		
Yes	101	25.8
No	291	74.2
Chronic disease		
Yes	39	9.9
No	353	90.1
Functional status		
Working	47	12.0
Ambulatory	272	69.4
Bedridden	73	18.6
Model of Rx initiation		
Hospitalized	376	95.9
Ambulatory	16	4.1
Type of resistance		
Mono resistance	199	50.8
MDR &XD	193	49.2
BMI		
<18.5 kg/m2	286	73.0
>=18.5	106	27.0
Rx modified		
Yes	7	1.8
No	385	98.2
Registration group		
Previously not treated for TB	42	10.7
Previously treated for TB	350	89.3

Among 392 MDR TB patients 27.3% had baseline infiltration and nearly 41% had baseline cavitations **(Figure 3)**

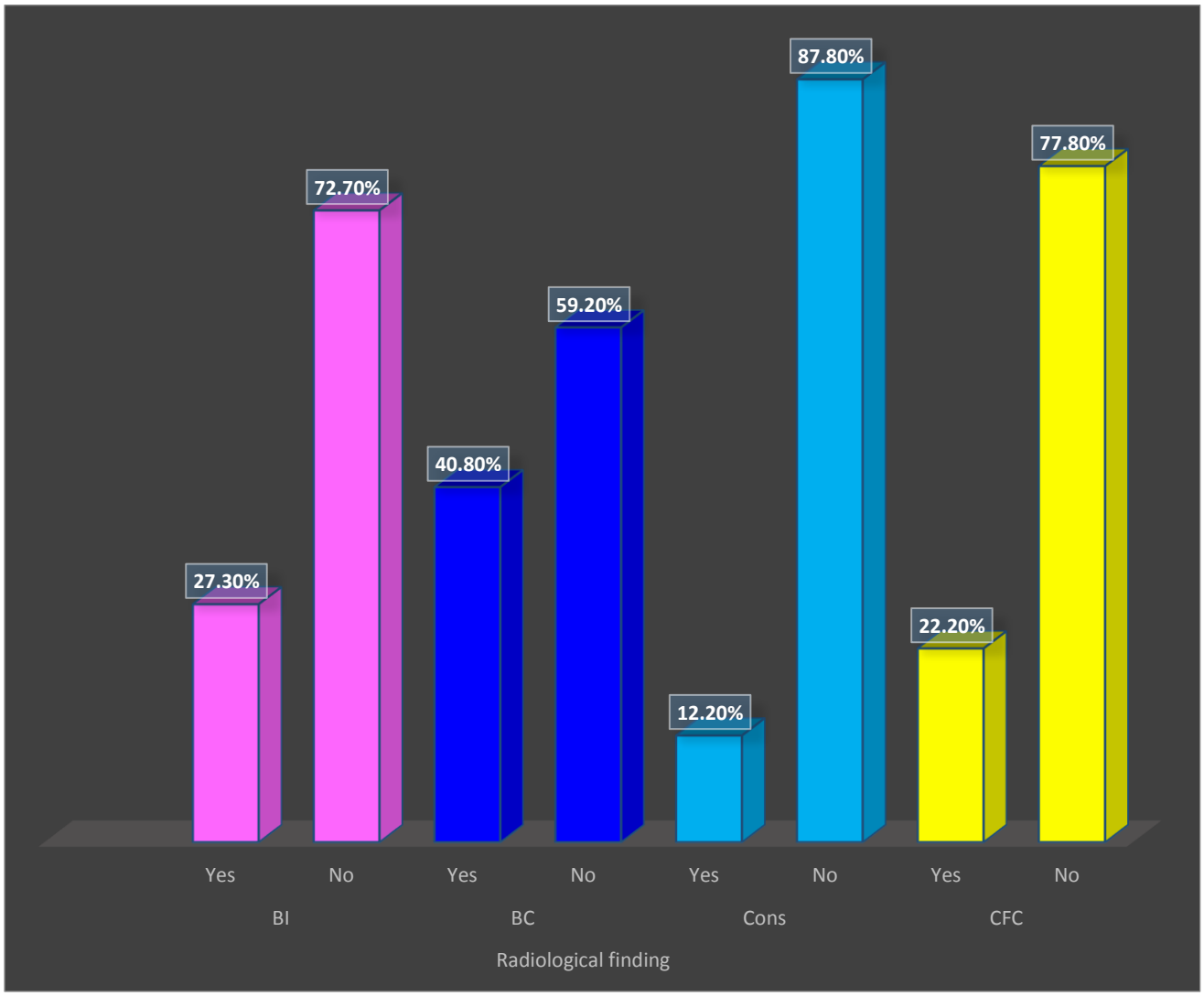

Figure 3 radiological findings of MDR patients at the baseline in Amhara Regional State Public Hospitals, September 2010 to December 2016

Among 392 MDR patients,98 (25%) had complication. Of these 41 (41.84%)had pneumonia, 24(24.5%) had fibrotic change, 16 (16.3) had COPD, and 9% had pneumothorax **(Figure 4).**

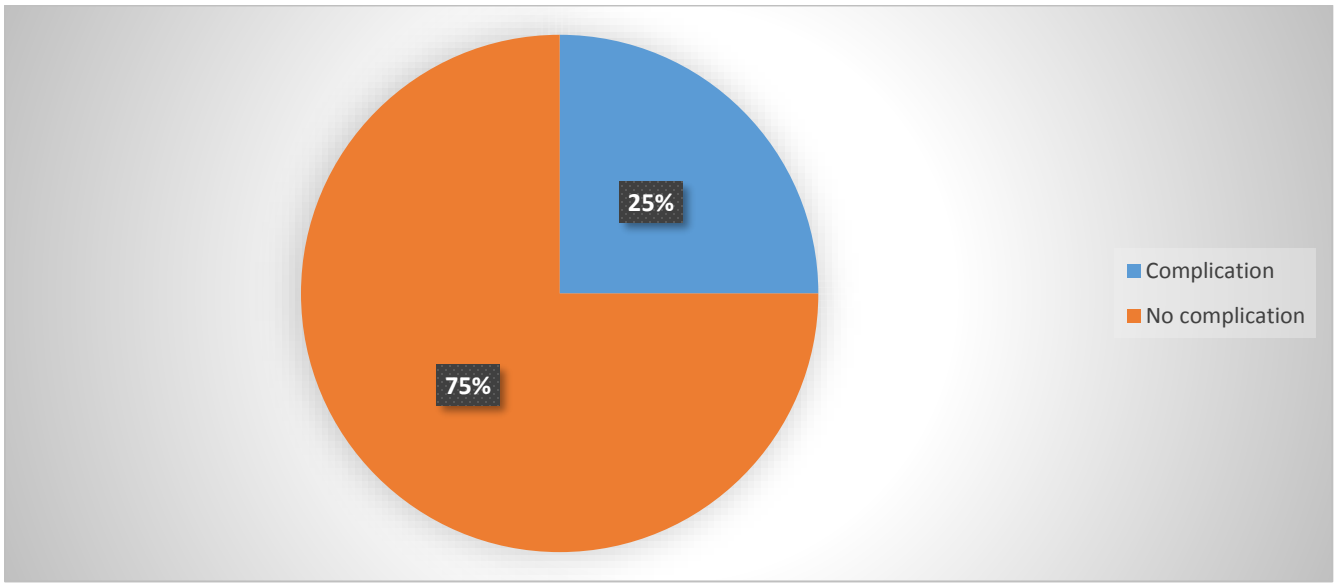

Figure 4 Complication status of MDR TB patients in Amhara Regional State Public Hospitals, September 2010 to December 2016

4.3.3 Diagnosis method and Treatment outcome of MDR TB patients

Next to cough fever is the most common presentation of MDR TB patients by 366 (93.4%) and followed by weight loss which accounts 365 (93.1%). Among a total of 392 MDR TB patients 136 (34.7%) had shortness of breath and around 285 (72%) had chest pain. About 319 (81.4%) and 305 (77.8%) of participants had history of fatigability and poor appetite.

Multi Drug Resistant TB patients were diagnosed by different methods. Among 392 MDR TB patients, 177 (45.2%) were diagnosed by MTB/gene expert, followed by LPA 139 (35.4%), by culture/DST 64 (16.3%) and clinically 12 (3.1%).

Among 392 MDR TB patients, 52 (13.3%) were censored and 340 (86.7%) were converted their culture.

The overall cure rate among MDR TB patients were 55.1% and 12 (3.1%) were completed (**Figure 5**)

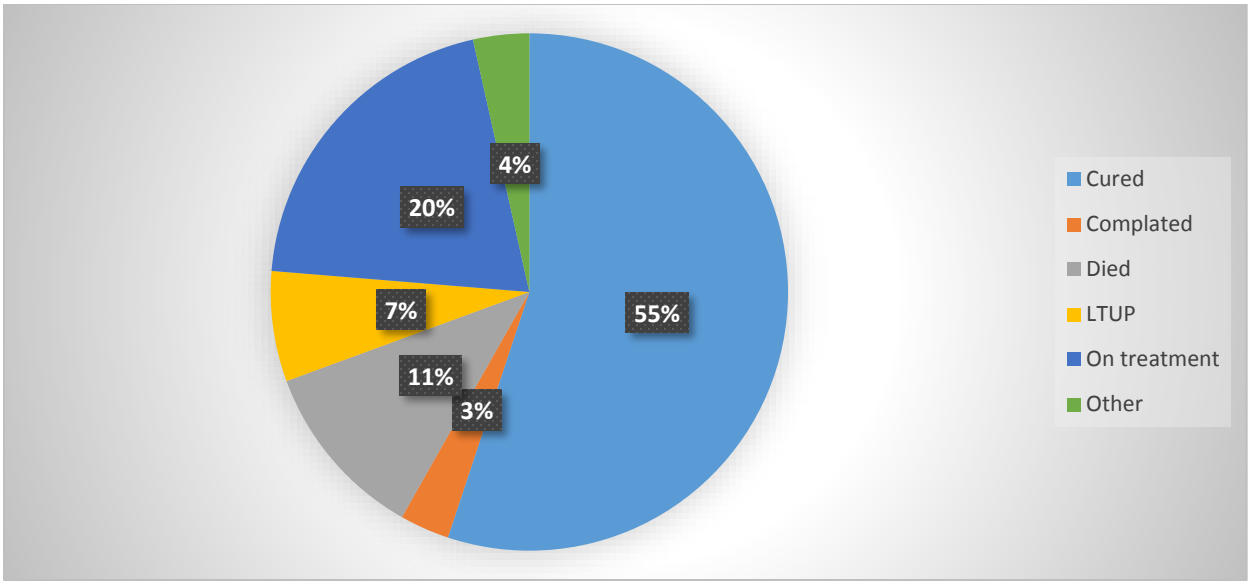

Figure 5 Overall treatment outcome of MDR TB patients in Amhara Regional State Public Hospitals, September 2010 to December 2016

4.4. Time to sputum culture conversion

Study subjects were followed for different periods which gave a total of 1000.6 person months (83.4 person years) observation. Median follows up period was 65 days CI (61-70).

The cumulative probability of survival on initial conversion at the end of 1 month were 0.89, at the end of 2months were 0.56,and at the end of 4 months were 0.19 **(Figure 6).**

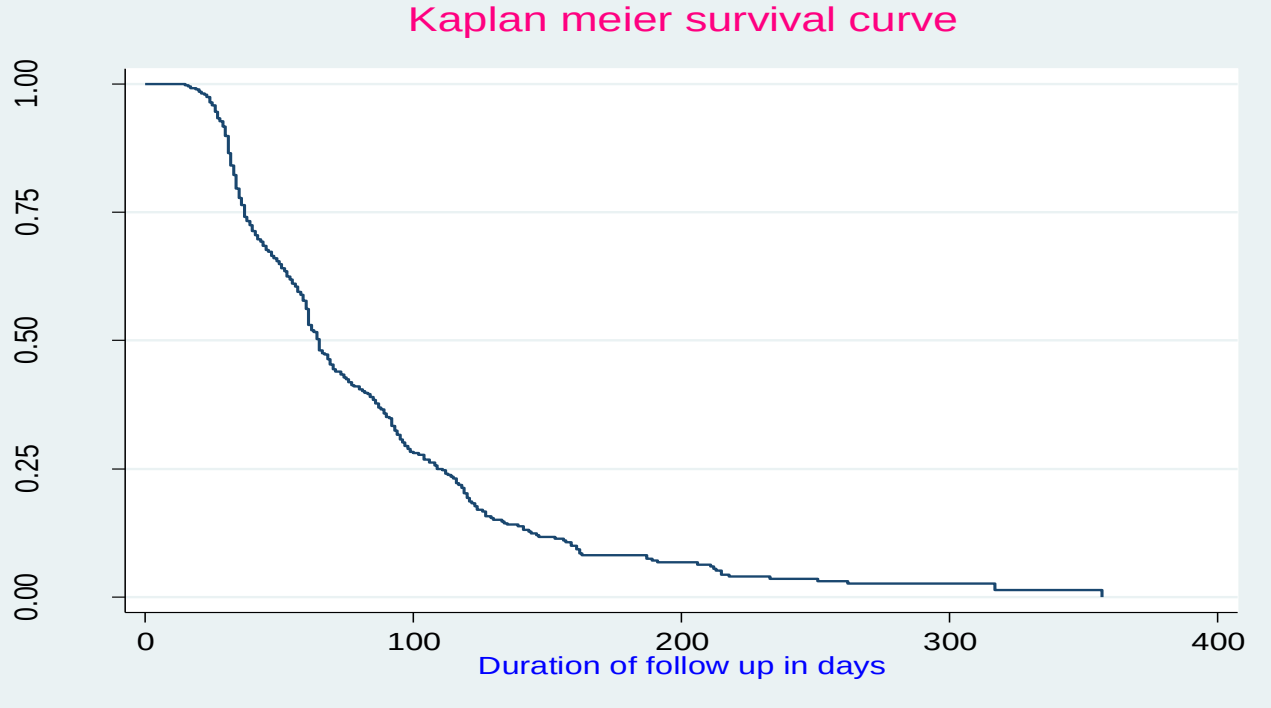

Figure 6 Kaplan-Meier curve showing survival of MDR TB patients on initial culture conversion in Amhara Regional State Public Hospitals, September 2010 to December 2016.

4.5. Predictors of initial sputum culture conversion using Log rank test

Differences in all key variables at baseline between strata were determined using log rank ($\chi 2$) test and assessed the equality of hazard for the different explanatory variables. According to the test results presence of infiltration (Chi2(16.23) =prob>Chi2=0.0001, cavitations (Chi2 (32.2) =prob>Chi2=0.000,consolidation(Chi2 (6.29) =prob>Chi2=0.0122, Fibrotic change (Chi2 (9.07) =prob>Chi2=0.0026,functional status(Chi2 (6.9) =prob>Chi2=0.0318, sputum smear grading(Chi2 (25.01) =prob>Chi2=0.0000and resistance type (Chi2 (4.94) =prob>Chi2=0.00263 were significantly associated with initial culture conversion time in patients on MDR treatment (P-value < 0.05).

Similarly the plot log-log of survival against log of survival time was done and the study indicated roughly parallel graphs for duration of follow up, thus proportional hazard assumption was met. There was an interaction between functional status and time

indicating possible violation of PH assumption. However, the Schoenfeld global test of the functional status satisfies the PH assumption (chi2 (2) = 2.45, Prob>chi2=0.294).

As the graph shows below mean survival time on culture conversion for patients who were bedridden had a median conversion time of 87 days. Whereas, those ambulatory and working patients had a median conversion time of 63 and 56 respectively and the difference was significant (p-value=0.0318) **(Figure 7).**

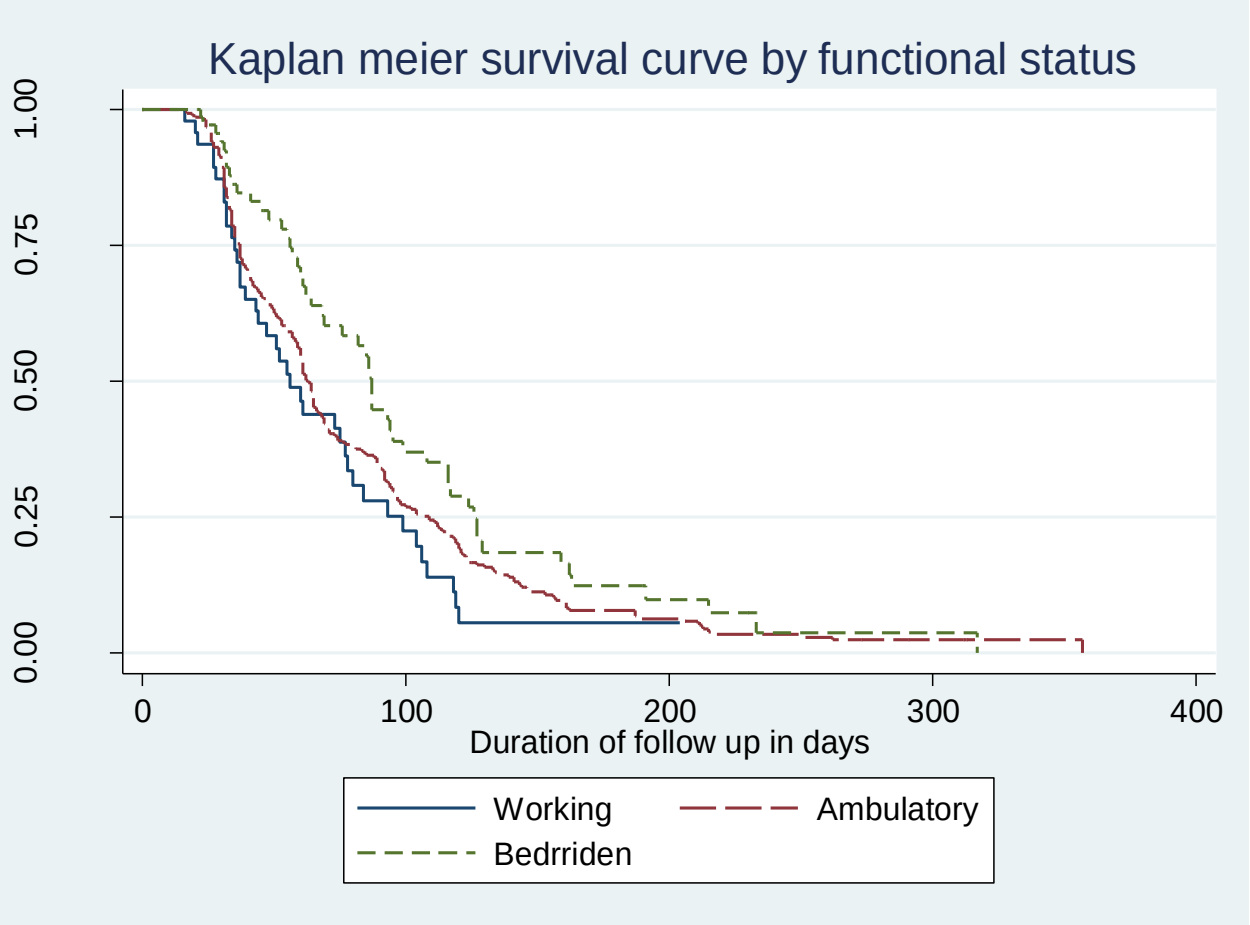

Figure 7 Kaplan-Meier curve of surviving MDR TB patients on initial culture conversion by baseline functional status in Amhara Regional Public Hospitals, September 2010 to December 2016.

The survival curve plotted below indicted that the estimated survival curves of hospital and the log rank test used for checking the differences in survival curve displayed. There was no overall difference between the survival curves of the hospitals as the log rank test supported the null hypothesis (log rank Chi-square (2) = 7, p= 0.2294).The median culture conversion in Gondar, Borumeda and Debre Markos were 65 CI (61-76), 63 (53-80) and 62 (42-76) days respectively **(Figure 8).**

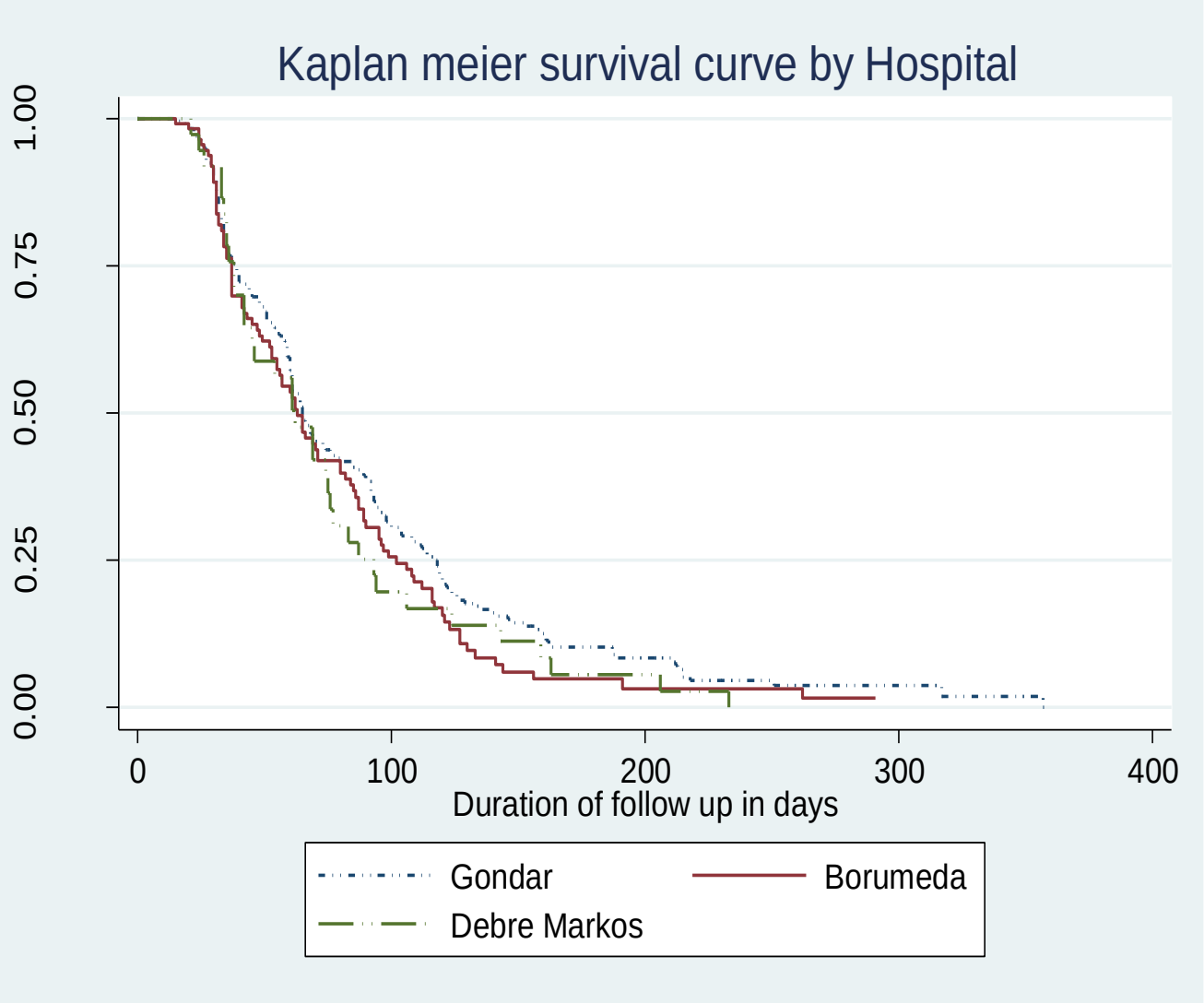

Figure 8: Plot of the probability of survival by hospital and the time of follow up (in days) among MDR TB patients in Amhara Regional State Public Hospitals, September 2010 to December 2016

Model comparison criteria

Based on Akaike Information Criterion, the univariate frailty with Weibull distribution and gamma frailty (AIC=396.82) model was more efficient than Cox-proportional hazard (AIC = 1859.41), parametric exponential model (AIC = 545.05) and other frailty models **(Table 4).** Thus, the inclusion of a frailty effect estimated was none statistically significant variance and indicates the absence of a heterogeneity or unobserved variability among hospitals. But, there is statistically significant heterogeneity among individuals (variance=1.56).

Table 4 Model comparison criteria for the different models using AIC

Model	Baseline hazard	Frailty	Variance	Log likelihood	AIC
Cox	Unspecified			-919.71	1859.41
Exponential Reg	Exponential			-261.89	545.05
Weibull Reg	Weibull			-200.99	425.99
Gompertz Reg	Gompertz			-237.33	498.66
Univariate frailty	Weibull	Gamma	1.56(P<0.001)	-185.41	396.82
Univariate frailty	Weibull	Inversegaussian	3.1(P<0.001)	-189.53	405.06

Goodness of fit test

Goodness of fit for the fitted model also performed using Cox Snell residual test and shows the model was adequate **(Figure 9).**

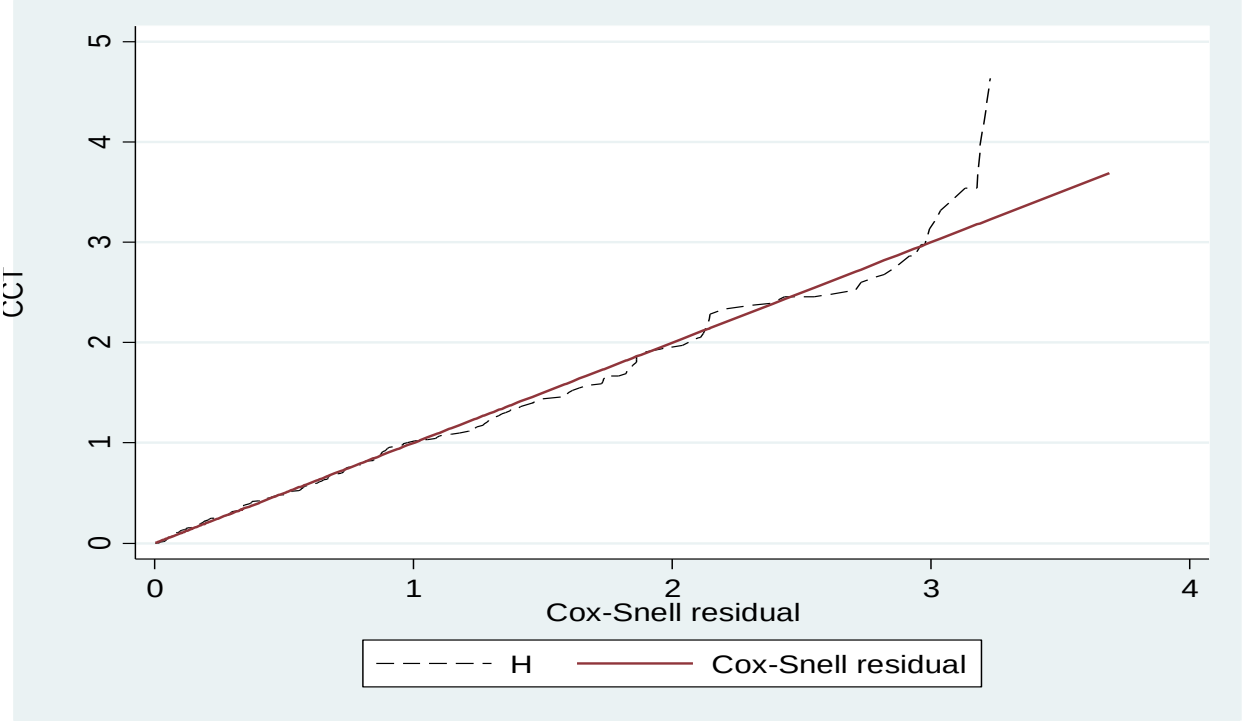

Figure 9 Goodness of fit test for univariate Weibull distribution gamma frailty model

Univariate frailty model analysis

Finding from bivariate analysis showed that alcohol drinking, type of resistance, baseline sputum smear grading, cavitations at baseline, baseline infiltration, baseline consolidation, chronic fibrotic change at the baseline, and baseline functional status were significantly associated with culture conversion time.

However, in the multi-variable analysis baseline alcohol drinking status, baseline sputum smear grading, baseline cavitations, and consolidation were remained statically significance predictors of time to sputum culture conversion.

The rate of sputum culture conversion among those who didn't drink alcohol at the baseline had 3.79 times as compared to alcohol drinkers**(AHR=3.79(CI:1.65-8.68)**).

The rate of sputum culture conversion among MDR TB patients whose baseline sputum smear grading +2 was decreased by 61%(**AHR=0.39(CI: 0.19, 0.79**) as compared to MDR TB patients whose baseline smear grading +1. Similarly, the rate of culture conversion among MDR TB patients whose baseline smear grading +3 was decreased by 70% (**AHR=0.30(0.14, 0.64))** as compared with those baseline sputum smear +1.

Regarding on x-ray finding MDR TB patients who had cavitations at the baseline decreased culture conversion time by 64% as compared to those MDR TB patients without cavitations **(AHR=0.36(CI:0.19,0.68)).** Similarly, the rate of sputum culture conversion among MDR TB patients who had consolidation at the baseline is decreased conversion time by 71% as compared to MDR TB patients who had no consolidation (**AHR=0.29(CI:0.13,0.69)).**

Table 5 Univariate Weibull distribution gamma frailty model for factors affecting time to sputum culture conversion among MDR TB patients in Amhara Region State Public Hospitals, September 2010 to December 2016.

Variable	Censored	Event	CHR 95%CI	AHR 95%CI
Baseline Alcohol history				
Yes	14	63	1	1
No	38	277	2.42(1.83,3.21)	**3.79(1.65-8.7)***
Type of resistance				
Mono resistance	34	165	1	1
MDR and XDR	18	175	0.72(0.58,0.89)	0.73(0.42,1.28)
Sputum smear grading				
Smear G-1	4	114	1	1
Smear G-2	9	53	0.65(0.47,0.89)	**0.39(0.19,0.79)***
Smear G-3	12	44	0.37(0.26,0.54)	**0.30(0.14,0.64)***
Cavitations				
No	24	208	1	1
Yes	28	132	0.52(0.41,0.64)	**0.36(0.19,0.68)***
Infiltration				
No	32	253	1	1
Yes	20	87	0.55(0.43,0.71)	0.76(0.38,1.53)
Consolidation				
No	48	296	1	1
Yes	4	44	0.57(0.42,0.79)	**0.29(0.13,0.69)***
Chronic fibrotic change				
No	40	265	1	1
Yes	12	75	0.63(0.48,0.82)	0.54(0.28,1.04)
Functional status				
Working	8	39	1	1
Ambulatory	23	249	0.8(0.5,1.1)	0.75(0.33-1.69)
Bedridden	21	52	0.5(0.4,0.8)	0.35(0.12,1.05)

*indicates p-value <0.05

5. Discussion

In this study the median culture conversion time was 65 days. Having previous history of MDR treatment, baseline alcohol drinking status, baseline sputum smear grading, radiological findings like cavity and consolidation were found to be determinants of time to sputum culture conversion in this study.

Median culture conversion time in this study was 65 days. This finding is in line with a study conducted in South Africa (22) and Georgia(20). However, this finding showed delayed conversion as compared with study conducted in Peru (36)with median conversion time of 59 days. In Peru (36)these DST results as well as any prior anti-TB drug exposure were taken into account when formulating the treatment regimen but in our study DST was done after start of treatment with some indication.

In contrast, our study showed that a rapid culture conversion time as compared with a multi centered study conducted in five countries Peru, Latvia, Estonia, Russia, and Philippines in which the median culture conversion time was 3 months (90days) and similarly, a study in Pakistan had a median conversion time of 191 days(11, 35). This might be explained by in defining the outcome variable, since in our study culture conversion time is explained by two consecutive negative culture results, whereas, the multicenter study defining outcome when five consecutive culture results becomes negative. The second possible reason might be a very small sample size used in Pakistan study(N=85). The third reason could be in the present study upon positive sputum smear microscopy and detection of Rifampicin resistance by MTB/Rif Xpert is used to place patients on standardized treatment regimen right from the beginning rather than waiting for DST results (35).

In MDR TB patients alcohol drinking were resulted in delayed culture conversion time. This finding is in line with a multi centered study conducted in five countries Peru, Estonia, Philip pines, Latvia and Russia (11). This might be explained by large number of MDR patients who drink alcohol had cavitations in the multicenter study (11).The second reason could be related to poor nutritional status, direct toxic effects of ethanol on the immune system or poorer adherence to anti-tuberculosis treatment (37, 38).The

third reason might be alcoholism causes drug resistance by decreasing immunity status(39).

Multi drug resistance TB patients whose smear +2 and +3 were statistically significant to time to culture conversion and resulted in delayed culture conversion time. This finding is in line with a study conducted in Latvia(17), Korea (34) and Indonesia (33).Patients with high smear grading had high bacillary load. Having a high bacillary burden suggests stronger infectivity and requires a longer isolation period and more intensive treatment. Thus, it needs time to clear the bacilli if the bacillary load is high (34). The second possible explanation could be the presence of high bacillary load is better associated with reduction in bacterial killing and sterilizing activity of anti-TB drugs. It may be natural that patients with a higher colony count take a longer time to convert sputum cultures. This result suggests the importance of early detection and rapid cure(40).

Multi drug resistance TB patients who had baseline cavitations had statistically significant effect on time to culture conversion and resulted in delayed conversion time. The negative association between time to sputum culture conversion and lung cavitations in our study is in line with studies conducted in China (31) and Pakistan (29). The possible reason might be presence of lung cavitations decrease penetration and antibacterial activity of drugs (41). In contrast to our finding, studies conducted in South Africa have found no significant association between lung cavitations at baseline chest X-ray and culture conversion time (30). The possible reason might be explained by a larger sample used in our study and the second reason might be proportion of HIV co-infected in this study were 4 times lower than the study in South Africa (30).

The presence of consolidation on chest radiography was associated with a longer time to initial sputum culture conversion as compared with MDR patients who had no baseline consolidation. Consolidation occurs through accumulation of inflammatory cellular exudates in the alveoli and adjoining ducts. The liquid can be pulmonary edema, inflammatory exudates, pus, inhaled water, or blood (from bronchial tree or hemorrhage from a pulmonary artery). This minimizing the response to MDR treatment and may delay culture conversion time (42). In contrast to this finding a study conducted in South

Africa revealed that there is no significant relationship between baseline consolidation and time to sputum culture conversion. This finding might be explained by a small sample (n=56) and the second reason could be in South Africa majority (88%) of participants were HIV positive and these groups were immune compromised. Since, radiological finding in immune compromised persons like HIV may not have sufficient lung finding (30).

Sputum culture conversion in MDR TB patients is an important routine indicator in monitoring the treatment outcome. Achieving more rapid sputum culture conversion can increase patients comfort by reducing duration of an inject able drug use and simplify a patient's therapy. In addition, from the public health perspective, reducing the time to sputum culture conversion is an important infection control measure because patients with MDR TB and positive sputum cultures are infectious and may transmit the disease to other persons, family members, and health care providers (17).

6. Strength and Limitation

Strengths of the study

- Our study incorporated a multi-center site,
- Implementation of frailty model estimation instead of a binary end point (logistic regression) of culture conversion was considered as the strength of this study.
- Handling interval censoring by using parametric survival analysis.

Limitation of the study

Since the data were collected from secondary source: some important predictors like HGB, BCG scar, and income were missed, which had a significant association with time to sputum culture conversion in other studies.

7. Conclusion and Recommendation

7.1. Conclusion

The time to culture conversion in our study was rapid.

Having previous alcohol drinking, high baseline sputum smear grading, presence of cavitations and consolidation were found to delay time to sputum culture conversion.

7.2. Recommendation

To Health care providers

- Close follow-up, attention and health education is important especially those who were alcohol drinker.
- It is better to give special attention for patients who have baseline cavitations, and consolidation.
- It is better to assess baseline sputum smear grading and provide great attention to those who had high bacillary load.

To MDR-TB wards

- It is better to fill documents and correct miss label charts and registration books

To researcher

- It is recommendable to conduct prospective follow up study including other independent variables (Anaemia, BCG scar, income).

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Annex

Annex I Data collection Check list

This checklist is prepared for the collection of socio-demographic, clinical, behavioral factors, and treatment outcome related information that are important for the assessment of outcome and predictors of time to sputum culture conversion in University of Gondar Hospital, Debre Markos hospital and Borumeda hospital. All these information were retrieved from the clients MDR-TB registration book and from individual patient card without mentioning the name of clients. This information was collected by health care providers (BSc nurse or Health Officer).

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Part one - Baseline variables

s.n	Variables	Labels
1	Patient identification code	Unique code----------
2	Name of hospitals	1.Gondar---------- 2.Borumeda---------- 3.D/markos----------
3	Age of patient in years	_____years
4	Sex	1. Male 2. Female
5	Address	Region----- zone------woreda-------kebele----
6	Place of Residence	1.Urban 2.Rural
7	Occupation	1. Unemployment 2.Goverment 3.None government 4.Private 5. Other--------
8	Religion	1. Orthodox 2.muslim 3.Protestant 4.Catholic 5. Other-
9	Baseline weight	___ in Kg
10	Baseline height	-------in centimeter
11	Educational status	1. No educated 2. Primary 3. Secondary 4. Tertiary
12	Marital status	1. Married 2. Never married 3. Divorced 4. Widowed 5. Other------
13	Baseline smoking	1. Yes 2. No
14	Baseline alcohol drinking	1. Yes 2. No
15	Presence of other chronic diseases	1. Yes 2. No 3. Unknown

16	If yes for Q 15then what are?	1. DM 2.HTN 3. CKD 4.Bronchial asthma 5. Other(specify)
17	Registration group	1. New 2. Relapse 3. After LTFP 4. After failure of first line treatment 5. After failure of retreatment 6. Other
18	Model of treatment initiation	1. Hospitalized 2. Ambulatory
19	Date of MDR-TB Diagnosis	dd/mm/yy ----/------/------
20	Date of MDR-TB treatment started	dd/mm/yy ----/------/------
21	Time of sputum culture converted	dd/mm/yy----/----/----
22	functional status at first admission	1. Working 2. Ambulatory 3. Bedridden
23	Type of resistance	1.mono resistance 2.poly resistance 3.MDR 4.XDR
24	To which anti TB drug patients resistance	1.R only 2.R& H 3.R,H,E,S
25	Laboratory Diagnosis confirmed by	1.MTB/RIF gene Xpert 2.LPA 3.conventionl DST
26	Any TB related complication	1. Yes 2. No
27	If yes to Q.25 type of complication	1. Pneumothorax 2. Pneumonia 3. Hemoptysis 4. Cor pulmonale 1. Other----------
28	HIV co-infection	1. No 2. Yes 3. Didn't test 4. Unknown
29	If yes for Q.28 CD4 cell count, at the beginning of MDR-TB treatment	------- count of cells/mm3
30	If yes for Q. 28 Did receive ART	1. Yes 2. No
31	If yes for Q.30 When did it start	---/---/--- dd/mm/yy, ------ Duration on ART in month
32	MDRTB Treatment regimen	1. cs-z-etho/pto-lfx-cm 2. cs-z-PAS-lfx-cs 3.other----------
33	Radiological finding	1. Cavity 2. Infiltration 3. Consolidation 4. Efusion5. Hilar LAP 6. Fibrotic change 7. Other
34	Baseline sputum smear grading	3+(>9 AFB/HPF) 2+(1-9 AFB/HPF) 1+(10-99AFB/100/HPF) Scanty (1-9 AFB/ HPF) Negative
35	Final treatment outcome	1. Cured 2.completed 3.died 4.LTF 5. transferred out

		6. On treatment
36	Symptoms at admission	1. Shortness of breath 2. Fever 3. Weight lose 4. Hemoptysis 5. Chest pain 6. Sweating 7. Fatigability 8. Other

Collected

by_____Signature _____Date _____

Supervised

by_____Signature _____ Date _____

Annex II: Declaration

I, the undersigned, senior MPH student declare that this thesis work is my original work in partial fulfilment of the requirement for the degree of Master of epidemiology and biostatistics.

Name: Temesgen Yihunie
Signature: _____

Place of submission: Institute of public health, College of Medicine and Health Sciences, University of Gondar.

Date of Submission: _____

Advisors

Name	Signature
1. ----------	_____
2. ----------	_____